REMARKS

Rejections Under 35 USC §102

Claims 5-8 and 10 are rejected under 35 USC §102(a) as anticipated by **Murata** et al. This rejection is respectfully traversed.

Murata et al. teach a method of treating choroidal neovascularization (CNV) by injecting a retroviral vector encoding TIMP-2 into the subretinal space overlying choroidal neovascularization lesions. In contrast, claim 5 is drawn to a method comprising the use of a lentiviral vector. **Murata** et al. do not teach or suggest a method of gene therapy involving the use of a lentiviral vector.

It is generally known in the art that a retroviral vector is unable to transduce terminally differentiated, mitotically inactive cells such as retinal and retinal pigment epithelial cells. For this reason target cells have to be stimulated to undergo cell division before transduction by retroviral vector. Moreover, since retroviral vectors can only transduce mitotically active cells, and as those cells are eventually cleared from the subretinal space, transgene expression is expected to be brief and the anti-neovascular effect

finite. In contrast, lentiviral vectors are able to transduce mitotically inactive cells.

The superior ability of lentiviral vectors over other retroviral vectors to transduce non-dividing cells was shown in Figure 4. As the lentiviral vectors employed in the present invention transduce mitotically inactive retinal and retinal pigmented epithelial cells *in situ*, transgene expression is expected to be prolonged and the anti-neovascular effect long-lived. This is supported by the results in Figure 5 that show sustained (> 200 days) biologic effect of a transgene delivered by the lentiviral vector and conferred no selective advantage for or against the transduced cells. The demonstration of sustained therapeutic effect prior to the stimulation of blood vessel growth reflects an exploitation of the biologic ability of lentiviral vectors to deliver therapeutic genetic information to quiescent, non-dividing cells and thus, would be useful not only in treating patients with active neovascularization, but also in preventing the development of blood vessels in patients predisposed to ocular neovascularization.

Hence, Applicant submits that **Murata** et al. do not anticipate claim 5 of the present invention because retroviral

vectors and lentiviral vectors each possesses different and distinct characteristics and biological function. **Murata** et al. do not teach or suggest each and every aspect of the present invention; indeed **Murata** et al. is teaching away from the instant invention. Accordingly, Applicant respectfully requests that the rejection of claims 5-8 and 10 under 35 U.S.C. §102(a) be withdrawn.

Rejections Under 35 USC §112, 1st Paragraph

Claims 5-10 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

Claim 5 is drawn to a method of inhibiting intraocular neovascularization by administering to the eye a lentiviral vector encoding a fusion protein of Mig and IP10. Claim 10 recites the lentiviral vector is administered into the capsular, vitreous or sub-retinal space. Claims 6-9 have been canceled.

The Examiner contends that the specification is only enabling for a method of inhibiting intraocular neovascularization in cornea by administering a lentiviral vector encoding Mig/IP10 fusion

protein. The specification does not provide enablement for a method of inhibiting neovascularization in any other intraocular tissues by administering lentiviral vector encoding any therapeutic gene into any target site in an individual having intraocular disease. Applicant respectfully disagrees.

Example 7 of the instant specification teaches a method of inhibiting corneal neovascularization by applying a lentiviral vector encoding a fusion protein of Mig and IP10 to the corneal tissues. Table 1 and Figure 34 disclose the resulting inhibitory effect on corneal neovascularization. The present invention, however, is not limited to inhibition of corneal neovascularization.

To further demonstrate that administration of the lentiviral vector of the present invention to the eye results in inhibition of intraocular neovascularization, 12 primates received a sub-retinal injection of a lentiviral vector encoding an anti-angiogenic molecule. As shown in the enclosed Declaration under 37 C.F.R. § 1.132, marked inhibition of the size, severity and time of onset of subretinal neovascularization were seen in the eyes treated with lentiviral vector encoding the kringle domains of the plasminogen gene. Taken together, results presented in the

specification and the Declaration indicate that intraocular neovascularization can be inhibited by administering to the eye a lentiviral vector encoding an anti-angiogenic molecule such as a fusion protein of Mig and IP10 or the kringle domains of the plasminogen gene.

The Examiner contends that the specification fails to disclose that intraocular injection of a lentiviral vector would transduce any intraocular tissue, since vitreous humor is a gelatinous substance that would hinder the transduction of target cells. Applicant respectfully disagrees.

Applicant submits that the present specification has shown the efficacy of lentiviral vectors delivered into the cornea or subretinal space. Example 5 teaches inhibition of intraocular cellular proliferation by intravitreally-delivered lentiviral vector (page 51, line 13 to page 52, line 13). Results shown in Figure 12 and Example 5 indicate that the function of lentiviral vector and transduction of target cells are not hindered when the lentiviral vector is delivered into corneal tissues or the subretinal space.

The Examiner also contends that the present invention is not enabled because (1) the underlying mechanism of retinal

degeneration is not well understood and there are no adequate therapies for these disease at present, and (2) the specification fails to disclose the role Mig and IP10 chemokines in the development of age related macular degeneration. Applicant respectfully disagrees.

Applicant submits that a patent applicant is neither required to show how the invention works nor required to know the reason or mechanism behind the invention. As discussed above, Applicant submits that results presented in the specification and the Declaration have clearly demonstrated that intraocular neovascularization can be inhibited by administering to the eye a lentiviral vector encoding an anti-angiogenic molecule such as a fusion protein of Mig and IP10.

In view of the above remarks, Applicant submits that the specification has provided sufficient enablement for a method of inhibiting intraocular neovascularization by administering to the eye a lentiviral vector encoding a Mig/IP10 fusion protein. The lentiviral vector can be administered into the capsular, vitreal or sub-retinal space. Accordingly, Applicant respectfully requests that the rejection of claims 5 and 10 under 35 U.S.C. §112, first paragraph, be withdrawn.

This is intended to be a complete response to the Office Action mailed November 7, 2003. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Feb 17, 2004

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
(713) 270-5361 (facs.)
badler1@houston.rr.com